REMARKS

Claims 17 and 19-23 were examined and stand variously rejected under 35 U.S.C. §112, first paragraph; §112, second paragraph; § 102(b) and (a). By amendment herein, claim 17 has been amended to make explicit in the body of the claim what was previously implicit in the preamble. The above amendment is made without intent to abandon any originally claimed subject matter, and without intent to acquiesce to any rejection of record. Entry thereof is respectfully requested.

Sequence Requirements

The specification has been amended to include sequence identification numbers where appropriate on page 47. The application now fully complies with the sequences rules. Hence, Applicants respectfully request withdrawal of this rejection.

Drawings

Drawings addressing the Draftsperson's form were submitted on November 4, 2002 (concurrently with an RCE).

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 17 and 21-23 remain rejected under 35 U.S.C. 112, first paragraph as allegedly not enabled by the specification as filed. While it is acknowledged that the specification enables recombinant SIN particles having a Gly-Gln substitution at position 160, it is alleged the specification does not reasonably provide enablement for (1) any and all recombinant alphaviruses that infect human dendritic cells or (2) any and all amino acid mutations at positions 158 to 162. (Office Action, page 3). In addition, the Examiner again cites Tucker and MacDonald as teaching that mutation of the alphavirus genome may produce "some unexpected results" that make the virus less efficient as a gene delivery vehicle. (Office Action, page 4).

The specification itself, along with the state of the art at the time of filing, strongly belie the Examiner's position. Thus, the Office has not met its burden of showing the specification as filed does not enable the invention as set forth in the claims.

Despite the failure of the Office to make a case for non-enablement, Applicants address why the claims, as pending, are enabled throughout their scope. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). Whenever the PTO makes a rejection for failure to teach how to make and/or use the invention, the PTO must explain its reasons for the rejection and

support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the Applicants' claim. The reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971).

The factors relevant to a determination of enablement are set forth in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

With this legal framework in mind, Applicants reiterate that the record as a whole is overwhelmingly clear that the claims are fully enabled by the specification as filed. Indeed, the Office has failed to establish a *prima facie* case of non-enablement with respect to any of the pending claims.

As noted above, the first step in an enablement inquiry is to determine the proper scope of the claims. In the pending case, the Office incorrectly asserts that the claims cover "any and all" alphavirus recombinant particles having mutations at one or more positions corresponding to amino acids 158-162 of E2 that infect human dendritic cells. (Office Action, page 3). In reality, the pending claims do not encompass "any and all alphaviruses," but, rather, specify that (1) the recombinant alphavirus particle comprises an amino acid mutation at one or more of 5 specified residues; (2) that the particle is capable of infecting human dendritic cells; and (3) the particle is not derived from ATCC # VR-25226. In other words, the claims specifically set forth both the structure and function of the claimed particles. When properly viewed as a whole, it is clear that all aspects of the pending claims are fully enabled by the specification.

With regard to the alphavirus source of the E2 sequence, the specification indicates that any suitable alphavirus (except ATCC # VR-2526) that contains an amino acid mutation (as compared to wild type of the selected alphavirus) in the specified region is contemplated. (See, e.g., page 4, lines 18-25). Exemplary alphaviruses are listed on page 20-21 of the specification. Furthermore, the amino acid sequences of many of these virus particles (including E2 sequences) were known at the time of filing. (See, also page 20-21 of the specification indicating ATCC Accession numbers for various sequences). Further, it would have been utterly routine in view of the teachings of the specification to align any alphavirus sequence with a SIN E2 sequence to determine which 5 residues in the E2 region should be targeted for mutation. (See, also page 5, lines 4-12). In sum, any alphavirus could be used as a starting material for the claimed particles and the region to be targeted for mutation easily identified in any of these alphavirus protein.

The specification also clearly teaches how to make amino acid mutations in the region corresponding to residues 158-162 of an E2 glycoprotein from any alphaviral source. As was

well-known in the art at the time of filing, proteins containing mutations could be designed or selected in a variety of ways, for example by functional analysis and/or by altering the nucleic acid sequence encoding the protein, as described in detail on pages 34-40 of the specification. Particles falling within the scope of the claims must have a mutation in at least one of only 5 residues. Making mutations at each of these 5 residues would have been utterly routine for a skilled artisan. Applicants remind the Office that even costly and time-consuming experimentation is not "undue" if the techniques are well known and set forth in the specification. (See, *United States v. Telectonics Inc.* 8 USPQ2d 1217 (Fed. Cir. 1988), holding that a specification setting forth one working embodiment and a method of testing other embodiments was enabling, even in the face of evidence that testing for other suitable embodiments would require approximately $50,000 and 6-12 months). In the pending case, the evidence establishes that it would be entirely routine to make one or more mutations in the 5 amino acid-region specified in the claims.

Moreover, armed with Applicants' specification, it would be absolutely straightforward to test any mutated alphavirus particle for its ability to infect human dendritic cells. In fact, such testing would be completely routine for a skilled artisan in view of the teachings of the specification. Methods of culturing human dendritic cells were well known and described in the specification as filed. (See, *e.g.*, Example 1). Techniques of testing an alphavirus particle for its DC-tropism include, but are not limited to, testing FACS analysis, titer analysis, use of reporter molecules, and the like. (See, *e.g.*, page 40; page 42-43 of the specification). Thus, the specification provides ample guidance as to identification and testing of alphavirus particles that are capable of infecting human DCs.

In brief, the specification plainly teaches one of skill in the art (1) how to identify suitable sequences from any alphavirus; (2) how to make a mutation in these sequences and produce alphaviral particles having a mutation in the specified region; and (3) how to demonstrate infection of human dendritic cells by said particles. Accordingly, the specification provides ample guidance as to how to make and use the claimed invention.

Applicants also remind the Examiner that affidavits by experts can be used to establish what the specification reasonably conveys to the skilled artisan. *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). Further, the Office must articulate adequate reasons to rebut a Declaration that properly used facts to arrive at a logically reasoned conclusion (see, *In re Alton, supra*). Dr. John Polo presents further evidence establishing that the specification satisfies the enablement requirement of Section 112 with regard to the pending claims herewith in the form of a Rule 132 Declaration:

> 5. It is my opinion that, as a technical matter, a skilled worker could have readily made and used the compositions of the pending claims in light of the

specification, together with the common general knowledge, tools and methods available as of the effective filing date of April 1999. It is further my opinion that the references cited by the Examiner (Tucker and MacDonald) do not teach or suggest problems with the enablement of the pending claims. I base these opinions on the facts set forth below; however, I call attention to the fact that it was considered routine experimentation at the time of filing to culture human dendritic cells and to introduce specific mutations in amino acid sequences. I also call attention to the fact that the specification provides abundant direction regarding testing the ability of an alphavirus particle to infect human dendritic cells. In drawing my conclusions, I have considered the nature of the claims, the quantity of experimentation required to practice the subject matter of the claims, the direction present in the specification, the state of the field at the time the application was filed, the teachings of the cited references and the level of skill in the art. ...

7. When the specification was filed, it clearly taught a typical scientist how to make and use recombinant alphavirus particles from a variety of alphavirus species, where the particles are capable of infecting human dendritic cells and contain an amino acid mutation at positions 158-162 (based on SIN numbering) of E2 (relative to the wild-type alphavirus source). Thus, I believe that a typical scientist would have understood the specification clearly described all of the various aspects of the claims and enabled a typical scientist to make and use the invention as set forth in the pending claims. I base this belief on the facts set forth below.

8. First, at the time the specification was filed, both the nucleotide and the amino acid sequence of the E2 proteins of a many alphaviruses were known and published. (See, for example, page 21 and background section of the specification). The amino acid sequences of any alphavirus that was not known could have been easily obtained by standard sequencing techniques using RNA isolated from alphaviruses. It was also known at the time of filing that Sindbis (SIN) was considered the prototype and model for other alphaviruses. (See, *e.g.*, page 2, lines 8-16 of the specification). In view of the teachings of the specification, it would have been routine for the skilled artisan to align and compare nucleotide and amino acid sequences from various alphaviruses and determine which amino acid sequences in any alphavirus corresponded to positions 158-162 of a SIN E2 protein. (See, *e.g.*, page 37 of the specification, describing alignment of SIN strains). Also, in view of the disclosure, a person of skill in the art would surmise that mutants in this region would be much more likely to exhibit DC-tropism. Accordingly, it is my opinion that using the teachings of the specification and state of the art, it would require only routine experimentation for a typical scientist to obtain suitable amino acid sequences from any alphavirus (for example by comparison with sequences disclosed in the specification) and use these alphavirus sequences as a starting point for making the claimed particles.

9. Second, in light of the teachings of the specification, it would have been routine for a typical scientist to mutate one or more of amino acid residues corresponding to residues 158-162 of E2. Methods of making amino acid

mutations were well known in the art and described, for instance in Example 1 (particularly page 34) of the specification. Further, the production and testing of a particular mutant at residue 160 is described in the specification. It would also have been routine to determine, by structural and/or functional analyses, which amino acids corresponding to 158-162 could be mutated to develop DC-tropic particles. In light of the teachings of the specification, I believe that a typical scientist would have known how to make and use alphavirus particles including mutations in the specified region of an alphavirus E2.

10. Third, it would have been routine to produce alphavirus particles having the claimed mutation(s) in residues 158-162 of E2. Methods of generating (packaging) recombinant alphavirus particles, for example, through co-transfection of complementing vector and defective helper (DH) molecules or by introduction of vector into stable packing cell lines, were well known at the time of filing. (See, also, page 23, lines 5 to 23 of the specification). Also well known were methods of performing site-directed mutagenesis that would target one of the residues at positions 158-162. Thus, it is my opinion that it would have been routine for the skilled artisan to make recombinant alphavirus particles having the claimed mutation(s) in positions 158-162 of E2.

11. Fourth, it would have been clear to a typical scientist how to test for the ability of a mutant alphavirus particle falling within the scope of the claims to infect human dendritic cells. (See, *e.g.*, page 42 of the specification). Methods of culturing human dendritic cells were known and described in the specification as filed. (See, *e.g.*, Example 1). Moreover, methods of testing the ability of alphavirus particle to infect these cells are described in detail in the specification and include, but are not limited to, testing FACS analysis, titer analysis, use of reporter molecules, and the like. (See, *e.g.*, page 40; page 42-43). Thus, it is my opinion that a typical scientist could have readily tested any recombinant alphavirus particle containing the claimed mutation, following the teachings of the specification.

In sum, when the *Wands* factors are considered, it is clear that the record establishes that the specification as filed fully enables the pending claims throughout their scope. Therefore, Applicants submit that this rejection should be withdrawn.

Tucker and MacDonald do not Establish Unpredictability

The references cited by the Office as allegedly demonstrating uncertainty and unpredictability of the effect of mutations in the E2 protein of an alphavirus are not relevant to the pending claims.

As noted above, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). Moreover, as detailed above, the presently claimed invention does not encompass

alphavirus particles having "any and all" mutations in E2. Rather, the claims are specifically directed to particles having mutations in one or more of 5 specified residues. Additionally, the particles must be tropic for human dendritic cells. Neither Tucker nor MacDonald address human DC-tropism or the particularly claimed mutations. Accordingly, on these bases alone, neither reference is relevant.

Nonetheless, for the sake of completeness, Applicants again address each reference in turn and discuss how each fails to establish unpredictability of the claimed invention. Unlike the claimed methods, Tucker is directed to SIN E2 mutants that increase neurovirulence and improve entry into neuroblastoma cells. There is no disclosure relating to infectivity of human dendritic cells or of mutations in residues 158-162 of an E2 polypeptide. Instead, the particular mutations tested by Tucker are at residues 55 and 172 of the E2 protein. (See, Abstract). For its part, MacDonald is directed entirely to VEE mutants (positions 76 and 116 of E2) that infect murine dendritic cells. (See, *e.g.,* Abstract and materials and methods). As described above, the burden is on the Office to provide evidence as to why it would require undue experimentation to practice the invention as claimed. MacDonald's and Tucker's disclosure in neuroblastoma or non-human dendritic cells and using different mutations does not rise to the level of establishing that the claimed invention is "unpredictable" or that it would require "undue experimentation" to practice the invention.

Dr. Polo also addresses Tucker and MacDonald and concludes:

> 12. It is further my opinion that MacDonald and Tucker are not relevant to the claimed recombinant alphavirus particles. Neither reference discloses infection of human dendritic cells with recombinant alphavirus particles, as required by all the pending claims. Furthermore, neither references describes, demonstrates or suggests what effect mutations in the claimed region of 158-162 would have on DC-tropism. In this regard, MacDonald discloses mutations only at positions 76 and 116 of E2, while Tucker discloses mutations at positions 55 or 172 of E2.

The question of enablement is what the specification teaches one of skill in the art. In this case, the specification teaches one of skill in the art how to make and use the precisely claimed invention. (see, *e.g.,* Polo Declaration attached hereto). Indeed, Applicants have pointed to specific disclosures (including working examples) of their specification that establish enablement. In addition, the supporting declaratory evidence of record clearly refutes any contention that the claims are not enabled. The references cited by the Office do not establish unpredictability.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 17, 19, and 21-23 under 35 U.S.C. § 112, second paragraph for being indefinite. (See Office Action, pages 4 and 5). Due to the well-established meaning of the terms used in the claims, Applicants believe that the claim language is definite.

It is axiomatic that definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular disclosure at issue, (2) the teachings of the art, and (3) the interpretation that would be given by one possessing an ordinary level of skill in the pertinent art the time the invention was made. *See, e.g., In re Marosi,* 218 USPQ 289 (Fed. Cir. 1983). Consequently, a claim that is understandable to one of skill in the art meets the requirements of the second paragraph of 35 U.S.C. § 112.

It is a well-established principal of patent law that the term "an" in patent parlance carries the meaning of "one or more" in open-ended claims containing the transitional phrase "comprising." See, *PPG Indus v. Guardian Indus Corp.* 48 USPQ2d 1351, 1353 (Fed. Cir. 1998); *Elkay Mfg. Co. v. Ebco Mfg. Co.,* 52 USPQ2d 1109, 1112, 1353 (Fed. Cir. 1999); *AbTox, Inc. v. Exitron Corp.,* 43 USPQ2d 1545, 1548 (Fed. Cir. 1997); Robert Faber ed., *Landis on Claim Drafting* 531 (3 ed. 1990).

With this legal framework in mind, Applicants note the claims would have been clear to the skilled artisan in view of the specification as filed. Specifically, it is clear from the disclosure that more than one mutation was contemplated:

> Within certain embodiments of the above, the alphavirus or recombinant alphavirus particle has an amino acid substitution in the E2 glycoprotein as compared to wild-type, for exmaple, at residues 158, 159, 160, 161, or 162. (page 5, lines 4-7 of the specification).

Thus, it is plain that the skilled artisan reading the specification would know that the claims are not limited to a single mutation at position 160. Dr. Polo concurs:

> 13. In addition, it is my opinion that it would have been clear to the skilled worker at the time the specification was filed that the claims encompassed mutations at one or more of the residues corresponding to residues 158-162 of an alphavirus E2 glycoprotein. It is clear from the specification, for example, on page 5, lines 4-12 that "an" amino acid substitution refers to one or more substitutions in the specified region.
>
> 14. Thus, it is my opinion that making and using recombinant alphaviruses of the claimed invention was a predictable art. I have no doubt that as of April, 1999 a person of skill in the art was capable of making the alphavirus mutants and testing them for the ability to infect human dendritic cells. Even if a mutant were inoperable for some reason, e.g., was not capable of infecting human dendritic cells, the skilled worker could have readily modified the mutant

according to known techniques. Undue experimentation would not be involved in determining which embodiments were inoperable.

Thus, it is clear that the claims encompass proteins having one or more mutations in the region specified.

Rejections under 35 U.S.C. §102

The Examiner has rejected claims 17 and 21 under 35 U.S.C. § 102(b) as being anticipated by Glasgow *et al.* (*Virology* 1991, Vol. 185, pp. 741-748). In addition, the Examiner alleges that claims 17 and 21 are anticipated by Glomb-Reinmund *et al.* (*J. Virol.* 1998, Vol. 72, pp. 4281-4287).

Pending claim 17 explicitly recites that the particles "infect human dendritic cell." Glasgow *et al.* and Glomb-Reinmund *et al.* do **not** teach virus particles capable of infecting human dendritic cells. Hence, claims 17 and 21 cannot be anticipated by Glasgow *et al.* and Glomb-Reinmund *et al.* and, accordingly, withdrawal of this rejection is respectfully requested.

III. CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

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